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amended claim 10 to recite wherein the substitution further includes a substitution includes a substitution of an amino acid residue selected from the group consisting of 68, 76, 104, 159, 212, 248 and 252. Support in the original specification is at least found at page 2, lines 18-35, page 11, lines 2, 6, 7, 8, 14, and 16-20; page 12, lines 11-20; page 13, lines 1-9 and 11-20, page 14, lines 1-12; page 15, lines 1-20, page 16, lines 1-20, page 17, lines 1-20, page 18, lines 1-19, page 19, lines 1, and 3-20; page 20, lines 1-4 and 6-20; page 21, lines 1-8 and 11-20; page 22, lines 1-4 and 6-9; 20; Tables 3 (Original Specification filed November 2, 2001 at pages 40-59), Tables 4 (Original Specification filed November 2, 2001 at pages 61-69), and Tables 5 (Original Specification filed November 2, 2001 at pages 71-76). Applicant submits no new matter has been added in the present amendments.

Priority/Specification

Applicant has amended the specification to cite the intervening application serial NO. 09/178,155, now United States Patent No. 6,312,936 as requested by the Examiner. As such, the Applicant requests that the request for further amending of the specification concerning priority be withdrawn.

Double Patenting

Claims 1-6, 8 and 10-12 were rejected under the judicially created doctrine of double patenting over Claims 1-26 of United States Patent No. 6,312,936. Claims 1-12 were also rejected under the judicially created doctrine of double patenting over Claims 1-22 of United States Patent No. 6,482,628. Applicant has provided a Terminal Disclaimer disclaiming the term of the patent beyond the term of the aforementioned patents. Applicant respectfully requests that the double patenting rejection be withdrawn.

Claim rejections 35 USC 112, Second Paragraph

Claims 10-12 were rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regarded as the invention. Claims 10-12 were rejected as indefinite as the Examiner submitted that the artisan could not know which amino acid sequence to

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which reference should be made. Applicant submits that the artisan would know which sequence reference was made. Applicant stated in the application that all of the residue positions correspond to positions of *Bacillus amyloliquefaciens* subtilisin (Original Specification at Page 2, lines 4-5, Page 26, lines 1-10, lines 13-15, lines 17-18). Further in light of Figs. 1-3, those skilled in the art will recognize that the residue positions recited in Tables 3-5 are the residue positions corresponding to those of *Bacillus amyloliquefaciens*.

Applicant additionally submits that Claim 10 has been amended to recite wherein the substitution further includes a substitution includes a substitution of an amino acid residue selected from the group consisting of 68, 76, 104, 159, 212, 248 and 252. Claims 11 and 12 have been cancelled. Applicants respectfully submit that the Section 112, second paragraph be withdrawn.

Claim rejections – 35 USC §102

Claims 1-6 and 10-12 were rejected under 35 USC §102 in view of Graycar, et al, (International Publication WO 95/10615). Applicants' currently amended claims recite a protease variant comprising substituting an amino acid at a residue position corresponding to positions 103, 232, 236 and 245 of *Bacillus amyloliquefaciens* subtilisins. Graycar, et al does not describe substitutions at positions 232, 236 and/or 245. Graycar, et al does not describe the combination of the residue positions 103, 232, 236 and 245 as set forth in the currently amended claims. Applicant respectfully requests that the 35 USC § 102 rejection be withdrawn.

Claim rejections - 35 USC § 103

Claims 8 was rejected under 35 USC § 103 over Graycar, et al, in view of Weiner, et al (U.S. Patent No. 5,589,373). Since claims 8 and 9 depend from claim 1, all the recitations of the Claim 1 should be considered in the rejection of claims 8 and 9. Applicants' currently amended Claim 1 recites a protease variant comprising substituting an amino acid at a residue position corresponding to positions 103, 232, 236 and 245 of *Bacillus amyloliquefaciens* subtilisins. Graycar, et al describes a variant hydrolase having a plurality of amino acid residues replaced in a precursor enzyme corresponding to position +76 in combination with residue positions +99, +101, +103, +104, +107,

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+123, +27, +105, +109, +126, +128, +135, +156, +166, +195, +197, +204, +206, +210, +216, +217, +218, +222, +260, +265, and/or +274 (Page 19, bottom paragraph to Page 21, top paragraph). Graycar, et al does not hint nor suggest substituting at positions 232, 236 or 245. Graycar, et al does not hint or suggest of the combination of the residue positions 103, 232, 236, and 245 as set forth in the currently amended claims. Applicant submits that Claim 1 as currently amended is patentable over Graycar, et al.

Claim 8 was further rejected over Graycar, et al, in view of Weiner, et al. Applicant submits that there is nothing in Weiner, et al that overcomes the deficiencies of Graycar, et al. Weiner, et al describes a purified metalloprotease of about 62 amino acid residues (Col. 5, line 51 to Col. 6, line 37; Claims 3 and 4). There is nothing in Weiner, et al, that hints or suggests of a protease variant comprising substituting an amino acid at a residue position corresponding to positions 103, 232, 236 and 245 of *Bacillus amyloliquefaciens*. Applicant respectfully submits that the 103 rejection over Graycar, et al in view of Weiner, et al be withdrawn.

Claim 9 was rejected over Graycar, et al, in view of Ghosh (U.S. Patent No. 5,677,272). Graycar, et al, has been discussed above. There is nothing in Ghosh, et al that overcomes the deficiencies of Graycar, et al. Ghosh describes compositions comprising a hydrolase having a plurality of amino acid residues replaced in a precursor enzyme corresponding to position +76 in combination with residue positions +99, +101, +103, +104, +107, +123, +27, +105, +109, +126, +128, +135, +156, +166, +195, +197, +204, +206, +210, +216, +217, +218, +222, +260, +265, and/or +274 (Col. 2, lines 1-10; Col. 14, line 58 to Col. 16, line 10). There is nothing in Ghosh, et al, that hints or suggests of a protease variant comprising substituting an amino acid at a residue position corresponding to positions 232, 236 and/or 245 of *Bacillus amyloliquefaciens*. There is nothing in Ghosh, et al, that hints or suggests of a protease variant comprising a combination of amino acid substitutions at residue positions corresponding to positions 103, 232, 236 and 245 of *Bacillus amyloliquefaciens*. Applicant respectfully requests that the rejection of claim 9 over Graycar, et al in view of Ghosh, et al be withdrawn.

Conclusion

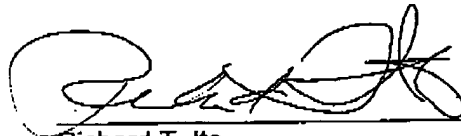
Applicants respectfully request entry of the above Amendment. Pursuant to 35 USC § 120, the Specification has been amended to recite the continuation status of this

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application, and its relations to the previous application filed by applicants. Applicants have submitted a terminal disclaimer with this amendment. Applicants have amended the claims to recite a protease variant comprising substituting amino acids at residue positions corresponding to position 103, 232, 236 and 245 of *Bacillus amyloliquefaciens* subtilisin. Applicant respectfully submits the rejections under 35 USC 112, second paragraph, 35 USC 102 and 35 USC 103 be withdrawn.

If the Examiner has any questions regarding the present application, he is encouraged to contact the undersigned.

Respectfully submitted,



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